Lasers in Surgery and Medicine 26:308–315 (2000)

Hyperbaric Oxygen and Photodynamic Therapy in the Treatment of Advanced Carcinoma of the Cardia and the Esophagus

Alfred Maier[1]* Udo Anegg,[1] Birgit Fell,[1] Peter Rehak,[2] Beatrix Ratzenhofer,[3] Florian Tomaselli,[1] Oliver Sankin,[1] Hans Pinter,[1] Freyja M. Smolle-Jüttner,[1] and Gerhard B. Friehs[1]

[1]Department of Surgery, Division of Thoracic and Hyperbaric Surgery, University Medical School, Graz, Austria
[2]Division of Biomedical Engineering and Computing, University Medical School, Graz, Austria
[3]Department of Anesthesiology, University Medical School, Graz, Austria

Background and Objective: **The photochemical reaction of photodynamic therapy (PDT) depends on the presence of molecular oxygen. Because of anoxic regions in tumor tissue and vascular shutdown during PDT, the efficiency is limited. Therefore, the use of hyperbaric oxygen, which increases the oxygen in tumor tissue, as well as the amount of singlet oxygen, may enhance the efficiency of PDT.**
Study Design/Materials and Methods: **After diagnostic work-up, photosensitization was carried out with a hematoporphyrin-derivate 2 mg/kg body weight 48 hours before PDT. The light dose was calculated as 300 J/cm of fiber tip. Twenty-three patients were treated by PDT alone and 29 patients received PDT under hyperbaric oxygen at a level of two absolute atmospheric pressures.**
Results: **Improvement regarding dysphagia and stenosis-diameter could be obtained in both treatment arms with no significant difference ($P = 0.43$ and $P = 0.065$, respectively). The tumor length also decreased in both groups and showed a significant difference in favour of the PDT/HBO group ($P = 0.002$). The mean overall survival was 11.3 months. The mean survival time for the PDT group was 8.7 months and for the PDT/HBO group 13.8 months ($P = 0.021$).**
Conclusion: **According to this pilot study, combined PDT/HBO represents a new approach in the treatment of esophageal and cardia cancer, which appears to have enhanced the efficiency of PDT. Lasers Surg. Med. 26:308–315, 2000.** **© 2000 Wiley-Liss, Inc.**

Key words: photodynamic therapy; hyperbaric oxygenation; esophageal carcinoma; cardia carcinoma

INTRODUCTION

Photodynamic therapy (PDT) for the treatment of advaned esophageal cancer has been approved in the USA, Finland, and United Kingdom. However, in other countries [1–3], it is still an experimental treatment and its role in clinical practice has not yet been established. This may be because of the complexity of the therapy, which requires the adaption of three components: light, a photosensitizing drug, and oxygen. Because of differences in vascular supply and lymphatic clearence from tumors and the retention of the photosensitizing drug by tumor cells, the photosensitizer is selectively retained in the tumor cells and interstitial tissue of the tumor. The photosensitizer will absorb light energy and produces singlet oxygen, which then destroys the tumor [4]. However, the photochemical reaction depends on the presence of molecular oxygen. It has been

*Correspondence to: Alfred Maier, Department of Surgery, Division of Thoracic and Hyperbaric Surgery, Auenbruggerplatz 29, A-8036 Graz, Austria.

Accepted 4 November 1999

shown that PDT only acts in the presence of oxygen. Because anoxic regions exist in many tumors, modalities increasing the amount of oxygen are necessary. In addition, as oxygen is consumed during PDT, too great fluence rates of light exposure will lead to oxygen depletion and should be avoided. However, there obviously is an optimal fluence rate, because a fluence rate that is too low may also lead to hypoxia, because a long exposure time is needed, and vascular shutdown may occur during PDT. Vascular shutdown certainly leads to hypoxia [4]. Therefore, the presence of molecular oxygen in tumor tissue is crucial for the effectiveness of PDT [5–7]. The use of hyperbaric oxygen to increase the availability of oxygen in hypoxic tissue is well known in the literature [8]. However, experimental studies by Dong et al. and Jirsa et al. [9,10] documented the enhanced effect of hyperbaric oxygen combined with PDT. Nevertheless, the combination of PDT and hyperbaric oxygen as a cancer treatment has never been established before in human beings. In a prospective, nonrandomized study, we assessed the use of PDT under hyperbaric oxygen, compared with PDT under normobaric conditions in patients with advanced cancer of the upper gastrointestinal tract.

PATIENTS AND METHODS

In a prospective study from January of 1995 to December of 1997, 52 patients with advanced cancer of the upper gastrointestinal tract who were not eligible for resection treatment because of poor performance status, functional and/or anatomic inoperability, and/or refusing surgery, were treated by PDT. In 29 patients, PDT was performed under hyperbaric oxygen conditions at a level of two absolute atmospheric pressures (ATA).

The protocol was approved by the institutional ethical committee of the medical faculty at the University of Graz. Informed written consent was obtained from each patient. A prospective randomization of the patients was not possible because of the variable availability of the hyperbaric chamber. However, the patients were selected in two treatment arms independent of the stage of disease, localization, histology, age, sex, dysphagia score, and Karnovsky performance status (KPS). The only selecting factor was the availability of hyperbaric oxygenation, 48 hours after photosensitization as the determined time for PDT.

Diagnostic work-up and clinical staging were done by means of barium esophagogram, esophagogastroscopy, bronchoscopy, computed tomography scans of the chest and abdomen, abdominal ultrasonography, and bone scan. Unfortunately, endoscopic ultrasound as the most reliable method for staging and postinterventional follow-up, was not available during the study period. Functional inoperability was confirmed by electrocardiogram, spiroergometry, blood gas analysis, and cardiac ultrasonography. At the time of admission, all patients complained about dysphagia of a semisolid diet (level 2) and liquids (level 3) within the past 3 months. Eight patients complained of aphagia (level 4) and were not able to handle their saliva. Weight loss of at least 5 kg within the past 2 months as well as insufficient nutrition was evident in most patients.

In the PDT group (Table 1), 21 patients were men and 2 were women (mean age, 68.6 years). Squamous cell carcinoma was evident in 11 and adenocarcinoma in 10 cases. In eight cases, tumor localization was seen in the distal third, five in the middle third, and one in the proximal third of the esophagus. In nine cases, the tumor was localized at the esophagogastric junction. By using TNM system of clinical staging, 19 patients were in stage III, and 4 patients in stage IV (T_3 = 9, T_4 = 14, N_1 = 9, N_2 = 14, M_0 = 19, M_1 = 4). The Karnovsky performance status was > 80 in 22 patients, only 1 patient had a KPS of 70. The dysphagia score before therapy was level 2 in 7 cases, level 3 in 11 cases, and level 4 in 5 cases. The mean stenosis diameter was 8.1 mm (range, 4–12 mm). The mean tumor length at the time of admission was 5.9 cm (range: 4.0 – 8.5 cm). In 23 patients, 34 PDT sessions (mean: 1.4; 4 cases had 2 sessions and 1 case had 3 sessions) were performed.

In the PDT/HBO group (Table 2), 21 patients were men and 8 were women (mean age, 67 years). Squamous cell carcinoma was seen in 14 and adenocarcinoma in 15 cases. In seven cases, the tumor localization was seen in the distal third, five in the middle third, and five in the proximal third of the esophagus. In 12 cases, the tumor was localized at the gastroesophageal junction. By using the TNM system of clinical staging, 25 patients were in stage III, and 4 in stage IV (T_3 = 13, T_4 = 16, N_1 = 14, N_2 = 15, M_0 = 25, M_1 = 4). All patients presented a Karnovsky performance status > 80. The dysphagia score before therapy was level 2 in 10 cases, level 3 in 16 cases, and level 4 in 3 cases. The mean stenosis diameter

TABLE 1. Photodynamic Therapy Group*

Age (yr)	Sex	Stage/histology	Dysphagia score prior/after PDT	KPS	Survival (months)	Tumor length prior/after PDT	Stenosis diameter prior/after PDT	PDT/session
85	f	T3N1M0G2; AD-Ca	3/1	90	16	5 cm/1.5 cm	9 mm/16 mm	2
75	m	T3N1M0G3; AD-Ca	3/1	90	13	4.5 cm/2 cm	9 mm/15 mm	1
75	m	T3N1M0G2; AD-Ca	3/1	90	15	6 cm/2.5 cm	9 mm/16 mm	2
66	m	T3N2M0G2; AD-Ca	3/1	90	13	5 cm/3.5 cm	9 mm/15 mm	1
67	m	T4N2M0G3; AD-Ca	3/1	90	11	4.5 cm/2.5 cm	9 mm/15 mm	1
58	m	T4N2M0G3; AD-Ca	3/1	90	5	6 cm/4.5 cm	9 mm/14 mm	1
83	f	T4N2M0G2; AD-Ca	4/2	70	1	5 cm/4 cm	4 mm/10 mm	1
73	m	T4N2M1G2; AD-Ca	3/1	90	5	4 cm/2.5 cm	7 mm/12 mm	1
61	m	T4N2M1G3; AD-Ca	3/1	90	4	5 cm/3.5 cm	7 mm/12 mm	1
69	m	T3N1M0G2; SC-Ca	3/1	90	12	5 cm/3 cm	9/15 mm	1
63	m	T3N1M0G3; SC-Ca	2/1	90	15	7 cm/4.5 cm	12 mm/16 mm	2
82	m	T3N1M0G3; SC-Ca	3/1	90	7	8 cm/5 cm	10 mm/16 mm	1
75	m	T3N1M0G3; AD-Ca	2/1	90	13	4.5 cm/2 cm	10 mm/15 mm	2
68	m	T4N1M0G3; SC-Ca	2/1	90	17	4 cm/1 cm	12 mm/16 mm	3
80	m	T4N1M0G3; AD-Ca	2/0	90	5	7 cm/5 cm	10 mm/15 mm	1
66	m	T3N2M0G2; SC-Ca	2/1	90	13	6 cm/4 cm	10 mm/15 mm	1
55	m	T4N2M0G2; SC-Ca	2/1	90	5	7 cm/5 cm	10 mm/15 mm	1
66	m	T4N2M0G2; SC-Ca	4/2	70	2	5 cm/5 cm	4 mm/10 mm	1
53	m	T4N2M0G2; SC-Ca	4/2	80	4	8.5 cm/6.5 cm	4 mm/10 mm	1
67	m	T4N2M0G2; AD-Ca	2/1	90	11	5 cm/2 cm	10 mm/15 mm	1
72	m	T4N2M0G2; SC-Ca	4/2	80	2	9 cm/9 cm	4 mm/10 mm	1
54	m	T4N2M1G2; SC-Ca	3/1	90	5	7 cm/5 cm	9 mm/15 mm	1
52	m	T4N2M1G2; SC-Ca	4/2	90	5	8.5 cm/6.5 cm	4 mm/10 mm	1

*AD-Ca, adenocarcinoma; SC-Ca, squamous-cell carcinoma; KPS, Karnovsky performance status. Dysphagia score, tumor length, and stenosis diameter were reported at the time of admission and 3 months after treatment.

was 8.8 mm (range, 4–12 mm). The mean tumor length at the time of admission was 5.6 cm (range, 4.0–8.5 cm). In 29 patients, 45 PDT sessions (mean, 1.4; 5 cases had 2 sessions, 2 cases had 3 sessions) were done.

Before PDT, dilation (Savary-Gillard device) and retrograde Nd:YAG laser desobliteration became necessary in 12 cases, because of severe stenosis (Fig. 1) only passable for the 3.2- or 5-mm bronchoscope (7 patients in the PDT group and 5 patients in the PDT/HBO group). A flexible guidewire was passed through the endoscope and careful dilation to at least 9 mm was done. The 7-mm bronchoscope was now passed over the guidewire and retrograde Nd:YAG laser disobliteration was performed. Perforation was excluded by esophagogram by using water-soluble contrast medium.

All patients received 2 mg/kg body weight of Photosan-3®, a hematoporphyrin polyester (Seehof Laboratory, Wesselburenkoog, Germany), administered intraveneously. In case of repetitive PDT several months later, a second injection of Photosan-3®, 2 mg/kg body weight, was done. PDT was carried out 48 hours after sensitization, by using a fiber with a 1-cm tip radial light diffusing cylinder (Photo Dynamic Therapy® HgesmbH, 1190 Vienna, Austria), which was inserted through the biopsy channel of the endoscope. For the treatment, the light-diffuser was closely applied to the tumor surface, although this was limited throughout the treatment because of esophageal wall motion, heartbeat, respiration, and sometimes coughing. The light dose was calculated as 300 J per cm of fiber. Light at 630 nm was applied by an KTP-Nd:YAG laser having a DYE module (Laserscope® Surgical Systems, Gwent, UK). Wavelength and light dose at the tip of the light diffuser (length, 1 cm) were controlled before and after PDT. In 29 patients, PDT was done under hyperbaric oxygen at a level of 2 ATA in the walk-in hyperbaric chamber (Fig. 2) at the University Hospital of Graz (Waagner Biro® AG, Graz, Austria). Oxygen was administered with the Scuba valve (Oxidem 2000®, Dräger, USA). Transcutaneous PO_2 levels of 500–750 mmHg (TCM™3, Radiometer Medical A/S, Copenhagen, Denmark) under hyperbaric oxygen at a level of 2 ATA, compared with $tcpO_2$ levels of 60–75 mmHg under normobaric conditions could be measured. According to Gray et al. [11], the oxygen pressure recorded at the transcutaneous electrode tends to be lower than the true arterial PO_2 because of oxygen consumption by the skin itself. Before HBO, all patients had an ear, nose, and throat check-up.

TABLE 2. Photodynamic Therapy with Hyperbaric Oxygen Group*

Age (yr)	Sex	Stage/histology	Dysphagia-score prior/after PDT/HBO	KPS	Survival (months)	Tumor length prior/after PDT/HBO	Stenosis diameter prior/after PDT/HBO	PDT/session
60	m	T3N1M0G2; AD-Ca	3/1	90	8	4.5 cm/2.5 cm	9 mm/15 mm	1
78	m	T3N1M0G3; AD-Ca	3/1	90	30	5 cm/0.5 cm	9 mm/16 mm	3
55	m	T3N1M0G3; AD-Ca	2/0	100	32	4 cm/1 cm	9 mm/18 mm	3
70	m	T4N1M0G2; AD-Ca	3/1	90	28	4 cm/1.5 cm	9 mm/16 mm	2
68	f	T4N1M0G3; AD-Ca	2/0	90	18	5 cm/2 cm	12 mm/18 mm	1
70	m	T3N2M0G3; AD-Ca	2/1	90	12	4 cm/1.5 cm	12 mm/16 mm	1
74	m	T4N2M0G3; AD-Ca	3/1	90	14	4.5 cm/1.5 cm	9 mm/15 mm	1
47	m	T4N2M0G3; AD-Ca	2/1	90	17	5 cm/2 cm	9 mm/15 mm	1
87	m	T4N2M1G3; AD-Ca	3/1	80	2	5 cm/3 cm	7 mm/14 mm	1
72	f	T4N2M0G3; AD-Ca	3/1	90	6	5.5 cm/4 cm	9 mm/14 mm	1
68	f	T4N2M1G3; AD-Ca	3/1	80	2	6 cm/5 cm	7 mm/14 mm	1
70	f	T4N2M0G3; AD-Ca	3/2	80	9	6 cm/3 cm	7 mm/14 mm	1
67	m	T3N1M0G3; SC-Ca	3/1	90	12	4.5 cm/1.5 cm	9 mm/15 mm	1
69	f	T3N1M0G3; SC-Ca	3/1	90	30	6 cm/2.5 cm	9 mm/16 mm	2
78	m	T3N1M0G2; SC-Ca	3/1	90	23	6 cm/2 cm	9 mm/16 mm	2
70	m	T3N1M0G3; SC-Ca	3/1	90	12	5 cm/2.5 cm	7 mm/14 mm	1
61	m	T3N1M0G2; SC-Ca	2/0	90	17	4.5 cm/1 cm	12 mm/18 mm	1
60	m	T3N1M0G3; AD-Ca	3/1	90	8	7 cm/5 cm	9 mm/15 mm	1
77	f	T3N1M0G3; SC-Ca	2/1	90	17	5 cm/1.5 cm	10 mm/15 mm	2
56	m	T4N1M0G2; SC-Ca	3/1	90	7	7 cm/5 cm	10 mm/15 mm	1
51	m	T4N1M0G2; SC-Ca	2/0	90	24	4 cm/1 cm	12 mm/18 mm	1
46	m	T3N2M0G3; SC-Ca	2/1	90	5	5 cm//2 cm	10 mm/14 mm	1
70	f	T3N2M0G3; AD-Ca	3/1	90	12	7 cm/3.5 cm	9 mm/15 mm	1
61	m	T4N2M0G2; SC-Ca	4/2	90	4	8 cm/6 cm	4 mm/9 mm	1
79	f	T4N2M0G2; SC-Ca	2/1	90	17	6 cm/2.5 cm	12 mm/16 mm	2
62	m	T4N2M0G3; SC-Ca	3/1	90	7	8 cm/5 cm	9 mm/15 mm	1
74	m	T4N2M0G3; AD-Ca	2/1	90	14	4.5 cm/1.5 cm	10 mm/16 mm	1
74	m	T4N2M1G3; SC-Ca	4/1	90	6	8.5 cm/6 cm	4 mm/14 mm	1
62	m	T4N2M1G3; SC-Ca	4/1	90	4	8.5 cm/6 cm	4 mm/14 mm	1

*AD-Ca, adenocarcinoma; SC-Ca, squamous-cell carcinoma; KPS, Karnovsky performance status. Dysphagia score, tumor length, and stenosis diameter were reported at the time of admission and 3 months after treatment.

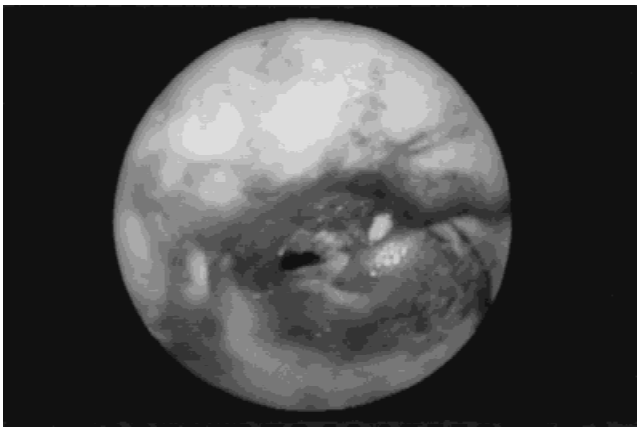

Fig. 1. Stenosis only passable with the 5-mm bronchoscope.

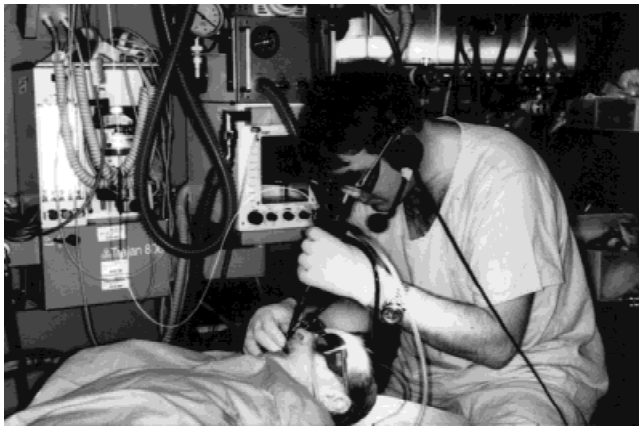

Fig. 2. Photodynamic therapy under hyperbaric oxygen.

Each treatment was done under short-term intravenous anaesthesia (Propofol 1% Zeneca®, Vienna, Austria) with endotracheal intubation and spontaneous breathing by using a scuba valve (Oxidem 2000®, Dräger, USA) combined with topical anaesthsia (Xylocain® 1%, Fieberbrunn, Austria). The monitoring consisted of electrocardiogram, noninvasive continuous blood pressure control and $tcpO_2$ (TCM™3, Radiometer Medical A/S, Copenhagen, Denmark). Two to 3 days after PDT, endoscopy was repeated and necrotic tissue was removed mechanically if necessary. The

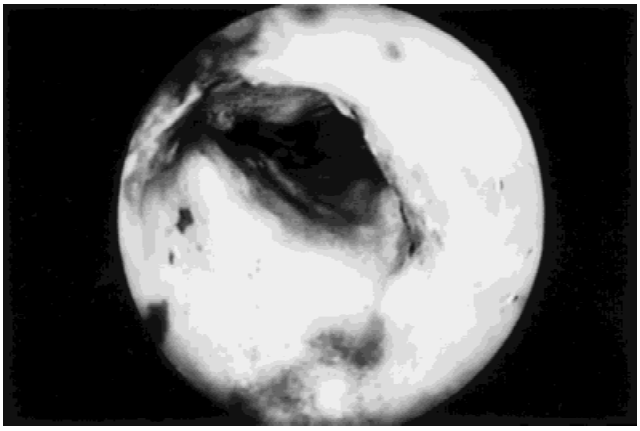

Fig. 3. Three-months follow-up of the tumor stenosis shown in Figure 1 after combined PDT/HBO.

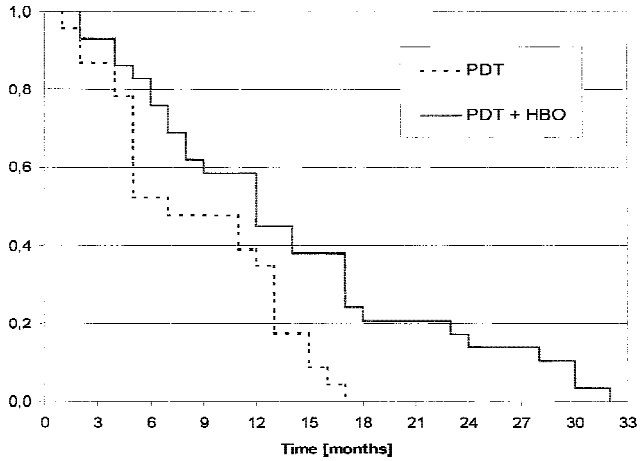

Fig. 4. Kaplan-Meier survival distribution after PDT and PDT/HBO.

depth of tumor necrosis was determined by the postdebridement increase in the luminal diameter measured at the maximal point of constriction. All luminal diameters were confirmed by noting the easy passage of graduated bronchoscopes (3.2, 5, 6, and 7 mm) and esophagogastroscopes (9, 11.6, and 14 mm) with known diameter, the easy passage of Savary-Gillard dilators of known diameter, or both. The patients then underwent repetitive endoscopy, first after 1 month and then once every 3 months (Fig. 3). Stage of disease, Karnovsky performance status (KPS), dysphagia score, diet, and complications were recorded at each follow-up control. Biopsy samples, tumor length, and minimal opening diameter were recorded at each endoscopy. Computed tomography scan of the chest and abdomen was performed every 6 months. An increase in tumor length and dysphagia at follow-up was the indication for repetitive PDT and or PDT/HBO treatment and was carried out within 3–27 months. No treatment was repeated within 3 months after the first PDT or PDT/HBO.

Statistical Analysis

Statistical analysis was performed by analysis of variance (ANOVA) and by chi-square test. Survival distribution was determined with the Kaplan-Meier survival table.

RESULTS

Statistical analysis for qualitative variables, performed by ANOVA and chi-square test showed no significant difference as to sex ($P = 0.15$), localization ($P = 0.29$), TNM stage (T, $P = 0.44$; N, $P = 0.35$; M, $P = 0.22$), grading ($P = 0.9$), dysphagia ($P = 0.52$) and Karnovsky performance status ($P = 0.33$) between both groups before entering the treatment schedule. Improvement regarding dysphagia could be obtained and a semisolid diet was at least possible in all patients after PDT or PDT/HBO. None of the patients needed further hospitalization caused by necessary nutritional support. At the 3-month follow-up, the dysphagia score in the PDT group could be lowered one level in 6 cases and two levels in 17 cases, and one level in 7 cases, two levels in 20 cases, and three levels in 2 cases in the PDT/HBO group. However, the chi-square test showed no significant difference ($P = 0.43$). After 3 months, the stenosis decreased in both treatment arms and showed a trend in favour of the PDT/HBO group ($P = 0.065$; chi-square). In the PDT group, the mean decrease in stenosis was 5.6 mm and in the PDT/HBO group 6.3 mm. The tumor length also decreased in both treatment arms and showed a significant difference in favour of the PDT/HBO group ($P = 0.002$; chi-square). In the PDT group, the mean decrease in tumor length was 2 cm, and 2.8 cm in the PDT/HBO group.

Survival

The mean overall survival time was 11.3 months (Fig.4). The median survival time for patients after PDT was 8.7 months, compared with 13.8 months after combined PDT/HBO. There was a significant difference in favour to PDT/HBO ($P = 0.021$; chi-square).

Complications

No major postinterventional complications related to PDT, HBO, and photosenitization of the

skin could be observed. No barotrauma of the ear or lung and no sunburn occurred. Minor complications such as postinterventional odynophagia (8 after PDT and 9 after PDT/HBO), fever up to 39°C in the afternoon of the interventional day (5 after PDT and 9 after PDT/HBO), and chest pain for 1 or 2 days (5 after PDT and 9 after PDT/HBO) could be observed. The 30-day mortality rate was 0%. Complications not related to the treatment occurred due to alcohol abuse in three patients, delirium tremens in two, and additional pneumonia in one case.

Because of tumor progression, we found 6 esophagotracheal fistulas in 2 cases after PDT at 5 and 17 months and in 4 cases after PDT/HBO at 4, 7, 14, and 24 months, respectively. All patients with this severe complication had a T_4 stage at the time of admission. All fistulas could be treated by stenting, by using self-expandable coated stents [Ultraflex™ Esophageal Stent System, Microvasive® Boston Sientific Corporation]. Additional tracheotomy in two cases, due to massive intratracheal tumor growth and dyspnea became necessary. However, endobronchial tumoricidial treatment was impossible because of coexisting major esophagotracheal fistula. Stenting and tracheotomy was done without any complications in these patients.

Because of tumor progression and bulky disease with external compression of the esophagus and gastroesophageal junction with resulting dysphagia, stenting with coated self-expandable stents [Ultraflex™ Esophageal Stent System, Microvasive® Boston Sientific Corporation] were performed, in two patients 14 and 17 months after PDT/HBO, and 16 months after PDT in one patient. One patient developed hemorrhage of the tumor, 18 months after PDT/HBO. Laser coagulation was succesfully performed, and the bleeding was stopped.

DISCUSSION

The poor prognosis of patients with advanced esophageal carcinoma is well known and reported in literature [12,13]. Local palliation with the aim to improve swallowing, short hospitalization, low complication rate, increase of KPS and quality of life, as well as economic aspects, especially in patients with a short life expactancy, are the goals of treatment of patients with advanced cancer of the cardia and the esophagus. PDT in the palliation of esophageal tumors as reported in the literature [14–16] is now a more and more accepted method and is used depending on its availability. However, there are some economic arguments against the use of PDT, especially in patients with a short life expectancy [17].

It should be emphasized that PDT provides the clinician with another modality that should be appropriately included in the overall management of the patient along with other modalities like dilation, Nd:YAG laser disobliteration, irradiation, and chemotherapy. The guiding principle is that PDT is more localized and selective than some other treatments but cannot be expected to entirely eliminate large, bulky tumor, especially outside the lumen or in lymph nodes. Considering all of these well-known facts in the treatment of advanced cancer of the esophagus and the cardia, new ways and modalities in fighting a cancer with a very poor prognosis and quality of life are necessary.

Photodynamic therapy involves the interaction of photosensitizers, light, and oxygen. Sensitizers in a low-energy state are initially excited by absorption of light. In this energetic state, it can react directly through a free radical mechanism or indirectly by means of molecular oxygen, which undergoes a spin-state transition to reactive singlet oxygen. Both pathways yielded potentially cytotoxic compounds, although the singlet oxygen process is thought to be predominant in PDT [18]. Oxygen has been shown to be crucial for hematoporphyrin-derivate photodynamic action in vitro [19], consistent with the hypothesis that singlet oxygen is the mediator of photodynamic cytotoxicity. Considering the interactions of the photosensitizers, light, and oxygen with singlet oxygen as the final common mediator of photodynamic cytotoxicity, it may be helpful to use methods to increase the oxygen tension in tissue to gain enhanced effectiveness on tumor cells.

According to the experimental studies by Dong et al. [9], the addition of HBO in PDT accelerates the photodynamic reaction processes by raising the transmission efficiency of light energy, increasing the quantum amount of oxygen and extending the effective distance radius of oxygen. The animal model by Jirsa et al. [10] showed the influence of HBO and PDT in tumor bearing nude mice. They concluded that the combination of HBO and PDT improve the efficiency of PDT by increasing the depth of tumor cell damage, by re-

ducing doses of sensitizers, or both. Another important phenomenon was found by Wieman et al. [20]. They showed that PDT induces reduced blood flow and causes a shutdown of tumor vessels resulting in hypoxia with decreased oxygen tension.

On the basis of these reported experimental studies by Dong et al., Jirsa et al., and Wieman et al. [9,10,20], the use of hyperbaric oxygen in this special field of cancer treatment could be the key to gain high levels of molecular oxygen in tumor tissue to increase the amount of oxygen as the main cytotoxic product.

Lambertson et al. [22] determined that, in a typical tissue, the arteriovenous oxygen difference rises to 350 mmHg when 100% oxygen is breathed at 3 ATA. If the blood flow to the tissues is reduced by a half, the corresponding values of capillary pO_2 will be 288 mmHg and 50 mmHg. Of course, the oxygen requirement of different tissues varies. Another factor is the vasoconstricting effect of HBO, which reduces the blood flow. However, effective cellular oxygenation can be accomplished at very low rates of blood flow when arterial pO_2 is very high. Furthermore, HBO improves the elasticity of the red blood cells and reduces platelet aggregation. This characteristic, combined with the ability of plasma to carry dissolved oxygen to areas where red blood cells cannot reach, has a beneficial effect on the oxygenation of many hypoxic tissues. However, general effects of HBO in human patients result in a decrease in cardiac output because of bradycardia rather than a reduction of stroke volume. Blood pressure remains essentially unchanged. Blood flow to most organs falls in correspondence to the decrease of cardiac output except on the right and the left ventricles of the heart. There is no impairment in function of any of these organs, because the elevated pO_2 more than compensates for the reduction in blood flow. Vasoconstriction may be viewed as a regulatory mechanism to protect the healthy organs from exposure to excessive pO_2. A very important phenomenon in this concept is that the vasoconstrictor response does not take place in hypoxic tissues [8]. Despite the many advances of HBO, there are also some toxic effects of oxygen when used as a drug. However, central nervous toxicity and pulmonary toxicity at pressures below 2.5 ATA when the duration of treatment does not exceed 90 minutes is rare.

The aims of local palliation determined by a decreased dysphagia score and tumor length, as well as increased quality of life could be obtained in both treatment arms with no significant difference concerning dysphagia and stenosis ($P = 0.43$ and 0.065, respectively). However, the tumor length showed a significant difference in favour of the PDT/HBO group ($P = 0.002$). These findings can be explained by the rising transmission efficiency of light energy which resulted in an increased destruction of tumor cells as described by Dong et al. and Jirsa et al. [9,10]. The significant difference in survival, in favour of combined HBO/PDT ($P = 0.021$) is very difficult to interpret, because many questions are impossible to answer in a nonrandomized pilot-study.

Although we assessed a small number of patients and there are no preexisting guidelines for combined PDT/HBO concerning the applied energy, the photosensitizer dose and the level of HBO, we had a mortality rate of 0%. It is evident that our protocol (photosensitizer 2 mg/kg body weight, light dose 300 J/cm of fiber and HBO at a level of 2 ATA) was associated with a very low complication rate. Although any therapeutic application of hyperbaric oxygenation is intrinsically associated with the potential for producing mild to severe toxic effects, the appropriate use of hyperoxia is one of the safest therapeutic procedures available in modern medicine [21,22]. Application of 100% oxygen at a level of 2 ATA is nontoxic, especially at a maximal time of 30 minutes. Our experience shows that the use of combined PDT/HBO involves minimal technical difficulties. All technical devices used such as endoscopes, light applicators, monitors, and perfusion-pumps functioned properly under hyperbaric conditions. We had no technical problems during the reported 29 combined PDT/HBO treatments.

Esophagotracheal fistulas in six patients occurred several months after PDT and PDT/HBO. However, in case of advanced esophageal carcinoma, it is difficult to distinguish between tumor- and treatment-related complications, especially if these occur several months after treatment. Nevertheless, we believe that there is an initial connection between treatment and the fistula incidence in our study. As risk factors for the development of esophagotracheal fistulas, T_4-stage and tumor localization in the proximal third of the esophagus were evident in our patients. Therefore, one should be aware to perform combined PDT/HBO in patients with T_4 carcinoma and signs of tracheobronchial tumor involvement at staging bronchoscopy.

Although the pilot study presented only includes a small number of patients, which does not allow one to draw definite conclusions, it indicates that combined PDT/HBO represents a new, safe, and feasible approach in the treatment of advanced esophageal carcinoma and can enhance the efficiency of PDT.

REFERENCES

1. Sibille A, Lambert R, Souquet J, Sabben G, Descos F. Long-term survival after photodynamic therapy for esophageal carcinoma. Gastroenterology 1995;108:337–344.
2. Karanov S, Shopova M, Getov H. Photodynamic in gastrointestinal cancer. Lasers Surg Med 1991;11:395–408.
3. McCaughan JS Jr., Photodynamic therapy versus Nd-YAG laser treatment ofendobronchial or esophageal malignancies. In: Spinelli P, Dal Fante M, Marchesini R, editors. Photodynamic therapy and biomedical lasers. New York: Elsevier; 1992. p 23–36.
4. Moan J, Peng Q, Sorensen R, Iani V, Nesland JM. Biosphysical fondations of photodynamic therapy. Endoscopy 1998;30:387–391.
5. See K, Forbes I, Betts W. Oxygen dependency of phototoxicity with haematoporhyrin derivate. Photochem Photobiol 1986;44:711–716.
6. Gomer C, Razum N. Acute skin response in albino mice following porphyrin photosensitization under oxic and anoxic conditions. Photochem Photobiol 1984;40:435–439.
7. Gibson SL, Hilf RC. Interdependence of fluence, drug dose and oxygen on haematoporphyrin derivative induced photosensitization of tumor mitochondria. Photochem Photobiol 1985;42:367–373.
8. KK Jain. Textbook of hyperbaric medicine. 2nd ed. Kirkland, WA: Hogrefe & Huber Publishers, Inc; 1996.
9. Dong GC, Hu SX, Zhao GY, Gao SZ, Wu LR. Experimental study on cytotoxic effects of hyperbaric oxygen and photodynamic therapy on mouse transplanted tumor. Chin Med J (Engl) 1987;100:697–702.
10. Jirsa M Jr, Pouckiva P, Dolezal J, Pospisil J, Jirsa M. Hyperbaric oxygen and photodynamic therapy in tumor-bearing nude mice. Eur J Cancer 1991;27:109.
11. Gray BJ, Heaton RW, Henderson A, Hutchinson DCS. In vivo calibration of a transcutaneous oxygen electrode in adult patients. In: Huch A, Huch R, Rooth G, editors. Contineous transcutaneous monitoring. advances in experimental medicine and biology. New York and London: Plenum Press; 1987. p 75–78.
12. Liang SW, Kwan HC, Maw HH. Management for patients with advanced T4 epidermoid carcinoma of the esophagus. J Surg Oncol 1996;62:22–29.
13. Segalin A, Little AG, Ruol A, Ferguson MK, Bardini R, Norberto L, Skinner DB, Peracchia A. Surgical and endoscopic palliation of esophageal carcinoma. Ann Thorac Surg 1989;48:267–271.
14. McCaughan JS Jr, Ellison EC, Guy JT, et al. Photodynamic therapy for esophageal malignancy: a prospective twelve-year study. Ann Thorac Surg 1996;62:1005–1010.
15. Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. Gstrointest Endosc 1995;42:507–512.
16. Scheider DM, Diemens M, Cirocco M, et al. Photodynamic therapy for the treatment of tumor ingrowth in expandable esophageal stents. Endoscopy 1997;29:271–274.
17. Ell C. Clinical photodynamic therapy: where is it heading? Endoscopy 1998;30:408–411.
18. Foote CS. Mechanisms of photooxygenation. In: Doiron DR, Gomer CJ, editors. Porphyrin localization and treatment of tumors. New York: Alan R. Liss; 1984. p 3.
19. Diamond I, Granelli SG, Mc Donough AF, Nielson S, Wilson CB, Jaenicke R. Photodynamic therapy of malignant tumours. Lancet 1972;2:117.
20. Wieman TJ, Mang TS, Fingar VH. Effect of photodynamic therapy on blood flow in normal and tumor vessels. Surgery 1988;194:512–517.
21. Clark JM. Oxygen toxicity. In: Bennett PB, Elliott DH, editors. The physiology and medicine of diving. 3rd Ed. London: Bailliere, Tindall and Cox; 1982. p 200–238.
22. Lambertson CJ. Effects of hyperoxy on organs and their tissues. In: Rubin E, editor. Extrapulmonary manifestation of respiratory disease. New York: Marcel Dekker; 1978. p 239–303.